Medical Melt Down
Thyroid Disease and ESRD

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Thyroid disease in ESRD

Thyroid Hormone Metabolism in ESRD

- ESRD a moderate to severe nonthyroidal illness that modifies Thyroid Hormone metabolism.

  Kaptein et al. Medicine 67:187-197, 1988

- Multiple other comorbid conditions that affect thyroid metabolism (DM, malnutrition, HPT, frequent infections)

- Certain thyroid diseases occur in increasing frequency in ESRD to include: goiter, thyroid nodules, and thyroid cancer

Goiter in ESRD

- Goiter - 0% of Pts in Great Britain to 58% in Utah
  Kaptein et al. Medicine 67: 187-197, 1998

	ESRD			Control		
Local	N	% Goiter	ATA	N	% Goiter	ATA
Denm.	40	60	7	40	0	?
Utah	53	58	0	?	8	?
Calif.	306	43	7	139	6.5	1.4
G.B.	25	0	?	?	?	?

Goiter in ESRD

- Kaptein 306 patients with ESRD on HD in L.A.

  Goiter is more frequent in those receiving HD > 1 year (50%) vs 37% in patients on HD < 1 year.

- Goiter did not relate to age, race , diabetes, TSH, PTH or Anti-microsomal levels

  Kaptein et al. Medicine 67: 187-197, 1998

- Thought to be from excess iodine total body stores-->decreased TSH production

  Konno et al. J Clin Endocrin Metab 78:393-397, 1994

Thyroid Nodules in ESRD

- More common in patients with ESRD
- In Japan thyroid nodules were found in 64% of 11 patients taken to parathyroidectomy for 2 HPT and in 55% OF 60 HD females compared with 21% of 224 normal females using 10 MHz HF ultrasonography

  Miki et al. J Surg Oncol 49:168-171, 1992

  Miki et al. J Surg Oncol 54:216-218, 1993
- Primary hyperparathyroidism has been shown to increase the risk for Thyroid nodules
- 351 patients with PHPT 20% had thyroid nodules at neck exploration but 47% had received prior radiation for benign conditions of the H&N.

  Prinz et al. Surgery 92:454-458, 1982

Thyroid Carcinoma in ESRD

- TC prevalence is higher in many studies of ESRD patients

- In the US 28,049 HD dependant patients the relative risk of Thyroid Ca (type unspecified) was increased 2.9 in females and 1.2 in males.

  Kantor et al. Am J of Epidemiol 126:370-376, 1987

- In the UK Thyroid Ca frequency was increased in females (15-44) by 4-8 times and 2 times in elderly pts.

  Brunner et al. Neph Dial Transplant 10(suppl 1):74-80, 1995

- In Japan Thyroid Ca found in 36% of 11 ESRD pts with 2HPT at surg compared to 11% at autopsy in control group. All those with thyroid Ca had elevated PTH levels compared to the rest of the group

  Miki et al. J Surg Oncol 49:168-171, 1992

Hypothyroidism in ESRD

- Primary hypothyroidism tends to be more common in ESRD patients.
- Range 0% in Austria to 9.5% in Michigan, whereas the general population has an incidence of 0.6-1.1%.
- In LA 2.6% of 306 ESRD pts had Hypothyroidism defined as a TSH >20mU/liter and a decreased TT4 and FTI
    - 88% were female
    - 75% were > 55 years of age
    - 50% had increased Anti-microsomal Abs
    - 50% had a goiter
    - 50% had DM
    - No relationship was found between hypothyroidism, goiter or DM
    - Kaptein et al. Medicine 67:187-197, 1988

Hypothyroidism in ESRD

- Iodine excess may play a roll in the increased frequency of hypothyroidism in ESRD.
- This is especially true in:
    1. Pts with an underlying iodide organification defect
       Takeda et al. Nephron 65:51-55, 1993
    2. Hashimoto's thyroiditis, previously treated Graves, or

       hemithyroidectomy
       Kaptein. Endo Rev Vol. 17, No 1:57, 1996
    3. Povidone-iodide may have induced hypothyroidism in

       CAPD pts. Gavin et al. West J Med 138:562-565, 1983

Hypothyroidism in ESRD

Screening

- Clinical suspicion must be kept high in patients at risk for hypothyroidism as medical mimics abound in ESRD pts such as DM, malnutrition and aging.

  Robuschi et al. Endoc Rev 15:142-153, 1987
- If you suspect hypothyroidism order a TSH
- TSH is the single most sensitive test of thyroid function in ESRD and patients with normal renal function
- Sensitivity: 2nd Generation=0.1, 3rd=0.05

  Normal (0.5 - 4.5 mU/L)
- If TSH is elevated confirm with FT4 or FTI
- **Primary hypothyroidism** TSH >20mU/L with low T4/T3

  Subclinical Hypothyroidism 4.5-20mU/L with normal T4/T3

  Recovery from nonthyroidal illness Low or High TSH low to normal T4/T3

Hypothyroidism in ESRD

Treatment

- T_4: Absorption (50-90%) is unaltered in ESRD patients

  Elimination is enterohepatic and also unaltered in ESRD

  Lim et al. JCI 60:522--534, 1977

- Initial dose is dependant on the cardiovascular status of the patient.

- Patients with known or suspected CAD should have initial doses reduced.

Hypothyroidism in ESRD

Treatment

- Average dose is 1.6ug/kg or 100 ug/Day
- START LOW GO SLOW (especially in our population)
- Start 25 ug/Day and increase dose every 3-6 weeks
- In patients with known or suspected CAD start 12.5ug/Day
- Recheck sTSH every 4-6 weeks

Hypothyroidism in ESRD

Treatment

What is the goal?

- Euthyroidism is determined by both sTSH and clinical signs and symptoms
- 10% of euthyroid ESRD patients have a TSH of 5-10 mU/L
- A conservative approach is to adjust LT_4 to this level unless otherwise indicated.
- Obtaining normal sTSH levels can lead to hyperthyroidism in ESRD patients and worsen or induce ischaemic heart disease.
- Total or free T_4 should not be used to adjust LT_4 doses

Kaptein et al. Medicine 67:187-197, 1988

Hypothyroidism in ESRD

Treatment

Failure to meet clinical goals with a dose of 1.6 ug/kg/day

- Noncompliance
- Interference with intestinal absorption or eneterohepatic circulation ($AlOH_3$, $FeSO_4$, cholestyramine, sulcralfate, kayexalate)
- Increased LT_4 degradation (Barbiturates, Carbamezapine, Rifampin)
- CAPD patients have an additional loss of 8-29 ug/Day

  Mandel et al. Ann Intern Med 119:492-502, 1993

Hyperthyroidism in ESRD

- Hyperthyroidism may occur at the same frequency as the general population.
- Only 10 cases have been reported in the literature.

Kaptein et al. Endocrin Rev 17:45-63, 1996

All were women

50% were > 50 YO

80% had goiters

80% had Graves' DZ

20% had MNG

30% had DM

Palpitations	(71%)
Weight loss	(71%)
A-Fib/flutter	(43%)
Weakness	(43%)
Irritability	(43%)
Tremor	(29%)
Heat intolerance	(29%)
Confusion	(29%)

Hyperthyroidism in ESRD

Diagnosis

- TSH levels have not been reported using 2nd or 3rd Gen assays
- TSH were < 0.01mU/L with no response to TRH in a group of hospitalized hyperthyroid patients.

  Spencer et al. J Clin Endocrinol Metab 70:453-460, 1990
- 9/10 patients with hyperthyroidism and ESRD had either elevated total or free T_4 but had normal or increased T_3 levels

  Kaptein et al. Medicine 67:187-197, 1988
- Currently a 2nd or 3rd Gen TSH is considered the most cost effective screen for hyperthyroidism with confirmation by either free T_4 and or TRH stimulation.

  Wheatley et al. Clin Endocrinol 31:39-50, 1989

Hyperthyroidism in ESRD

- Once hyperthyroidism is diagnosed the DDx and work up is the same as patients with normal renal function and includes:
  - Graves
  - MNG
  - Toxic adenoma
  - Thyroiditis
- As noted previously in the 10 reported cases of hyperthyroidism in ESRD patients 8 of 10 had Graves' and 2 of 10 had MNG.

Hyperthyroidism in ESRD

Therapy

- Supportive: Iodides
  Beta Blockers
- Definitive: Thionomides (Propythiouriacil, Methimazole)
  Radioiodine
  Surgery

Hyperthyroidism in ESRD

Therapy

Thionomides: Methimazole (MMI), Propylthiouracil (PTU)

- Block thyroid hormone production
- May decrease production of TSIs
- PTU also blocks conversion T_4 to T_3
- Improvement generally seen in 2 weeks and Euthyroid in 6-8

  weeks
- Most patients experience relief of symptoms but remission occurs in only 20-50% of those treated with Thionomides alone.

Hyperthyroidism in ESRD

- PTU: dose and efficacy is unchanged in ESRD patients

  Dose: 100-150mg q 8 hours
- Methimazole: dose and efficacy unchanged in ESRD but

  Methimazole is not protein bound and should

  therefore should be dosed after hemodialysis

  Dose: 20-30mg q Day after dialysis

Cooper et al. Arch Intern Med 147:785-786, 1987

Hyperthyroidism in ESRD

Therapy

- Surgery - Subtotal Thyroidectomy Indications:
  1. Failure of antithyroid therapy or refusal of radioiodine
  2. Graves' patients who are either young or pregnant
  3. Large compressive or obstructive glands
  4. Thyrotoxic patients with nodules suspicious for Cancer after FNA
- To prevent bleeding and Thyrotoxic crisis patients are made Euthyroid with Thionomides prior to surgery
- They are then given iodides (5 drops of Lugol's) 7-10 days before surgery

Hyperthyroidism in ESRD

Therapy

Radioactive iodine (^{131}I) ablation results - similar to surgery without operative complications.

- **Advantages:** Simple, effective and economical
- **Disadvantages:**
  - Hypothyroidism (40-70% at ten years)
  - Post ablation thyroiditis (7-10 days after ablation)
    - exacerbates obstructive/compressive symptoms
  - Contraindicated in pregnancy
  - May exacerbate ischaemic CAD

Harrison's P.I.M. 13th Ed. pp 1945

Hyperthyroidism in ESRD

Therapy

Effectiveness:

- Improvement is generally seen in 4-5 weeks and maximal effect obtained at 2-3 months
- 80-90% become euthyroid or hypothyroid
- Nearly all ablated patients eventually become hypothyroid and as such should be followed biannually with TSH
- Some authors recommend starting ablated patients on 100 uG of LT4 per day 1 week after the procedure to help prevent the patients development of hypothyroidism

^{131}I Administration

Iodide Metabolism:

- Removal is primarily by renal excretion

  Beckers et al. J Clin Endocrinol Metab 29:293-296, 1969
- Clearance of urinary Na ^{131}I is 25-35% of CrCl in normal patients.
- Patients with severe renal failure (4-11cc/min) Na ^{131}I clearance was found to average 50-57% of CrCl

  Kaptein et al. Endocrin Rev 17:45-63, 1996
- 10mg iodide loads were given to patients with normal CrCl and CrCl of < 44cc/min. At 24 hours 56% of the iodide was excreted with normal renal function vs 11% with CRI.

  Sato et al. Acta Endocrino 126:253-259, 1992

^{131}I Administration

- In ESRD Na ^{131}I clearance depends on the type, frequency, and duration of dialysis therapy
- Clearance rates of Na ^{131}I averaged 154cc/min during hemodialysis vs 25-35 ml/min in normal patients. So rapid clearance occurs only 5-7% of the week

  Kaptein et al. Endocrin Rev 17:53-54, 1996
- Half life between dialysis treatments is dependant on residual renal function
- Therefor Na ^{131}I clearance is dependant on the interval between administration and the next HD treatment
- No Na ^{131}I ablations have been reported in PD patients but

  Na ^{131}I clearances for 42 consecutive CAPD exchanges was found to be similar to that in normal patients. (CCPD, CIPD not studied)

  Oddie et al. J Clin Endocrinol 31:277-282,1970

^{131}I Administration

- Recommended dose of Na ^{131}I for Graves' is 0.2mCi/g of thyroid tissue. For MNG recommended does is 29.9 mCi.
- Total amount of isotope delivery is determined by:

  Delivery ^{131}I = (Dose X Thyroid weight / 24 RAIU)

- Thyroid weight is estimated by palpation and or ultrasound
- 24 RAIU: 7-8.0 uCi Na ^{131}I ingested and 24 hours later after technetium injection the thyroid is scanned and uptake determined. Normal (8-30%)

^{131}I Administration

- Thionomides are stopped 4-6 day prior to Na ^{131}I administration
- All iodine containing skin antiseptics are stopped 1 week prior
- Na ^{131}I is given after the last treatment prior to the weekend
- Upon return in 48 hours:
  - Dialysis in an isolated room
  - Minimum 3 feet from other people
  - Use routine HD orders
  - Tape effluent hose to the drain to insure aerosolization
  - Dialysis technicians may go through their usual routine but should not stay in the room when not actively working on the patient or machine

^{131}I Administration

- Prior to patient arriving the Radiation officer should take background radiation levels in the isolation room.
- After hemodialysis the officer should re-scan the background levels, the HD equipment and the technician
- Kidney and tubing are then placed in a freezer for 40 days and then disposed of per usual radioactive material protocol
- The HD machine should then be placed in rinse cycle over night and can may be reused the next day.
- Two prior studies using the above method found no radiation exposure to equipment or technicians in patients with MNG and ESRD
- These two studies showed the following:

Na ^{131}I in MNG

- Am J of Nephrol 13:214-217, 1993
- 38 YO BF on HD for three years then Diagnosed with hyperthyroidism
- SX: 5 # wt loss, palpitations, labile hypertension, heat intolerance
- Labs: TSH=0.26 (0.4-3.8) 24 RAIU = 37.5%
  TT4=9.8 (5.5-11.5) Gland wt est = 55 grams
  FT3=326 (90-190)
- Thyroid scan --> MNG
- 3 hours after hemodialysis ingested 14.7 mCi
- Measured radiation uptake was found to be maximum at 10 hours post exposure.
- Minimal exposure to the dialysis equipment and bedding was noted
- physical half life of the isotope was calculated to be 8.05 days.

Na ^{131}I in MNG

- AJKD 31:698-700, 1998
- 76 YO F ESRD 2 DM on HD for 1 year
- SN/ Sx: afib with RVR, proptosis, slight goiter on exam
- Labs: TSH = <0.05
  FT3 = 303 (230-420)
  FT4 = 1.4 (0.7-1.8)
- Initially thought to have euthyroid sick syndrome -->anxiety, tremors, insomnia, proximal muscle weakness. Labs repeated showed a FT4 of 2.3 and a TSH still at <0.05.
- Thyroid scan consistent with MNG
- Started on PTU 100mg PO TID
- One month later TSH=1.72, FT4=1.2

Na ^{131}I in MNG

AJKD 31:698-700, 1998

- Received 28.26 mCi of Na ^{131}I
- Given HD 24 hours later.
- Post Tx there was no significant radiation exposure to the techs, or machine and after rinsing during the night the HD machine was able to be used the following morning.

- References: See Below